Collaborative Project to Study Synaptic Complex after TBI Receives $2.6 Million NIH Grant

Daniel J. Liebl, Ph.D., professor at The Miami Project to Cure Paralysis and co-director of the University of Miami Miller School of Medicine’s Medical Scientist Training Program (M.D./Ph.D.), was recently awarded a $2.6 million R01 grant from the National Institutes of Health for his application titled “Stabilizing the tripartite synaptic complex following TBI.”

This award will support the continuation of a collaborative project between scientists at The Miami Project, the Department of Neurological Surgery and the Dr. John T. Macdonald Foundation Department of Human Genetics. The project will bring to fruition Dr. Liebl’s previous work that identified specific cells, receptors, and molecules — potential therapeutic targets — involved in synaptic loss after traumatic brain injury (TBI).

Dr. Liebl and his team first established an understanding of how a focal TBI results in the reduction of synapses, the distinct cellular units where neurons transmit signals between each other. The genesis for the project came from the observation that TBI induces loss of synapses in brain areas...
distal to the injury site that had previously seemed mildly affected by cell death and other traditional measures of injury.

Each neuron contains hundreds to thousands of synapses that are dynamically pruned during development in a consolidation process that stabilizes in adulthood — unless it is inappropriately reawakened, as Dr. Liebl’s work has demonstrated, by an insult such as TBI.

**Molecular Drivers of Synaptic Damage**

The work began in pre-clinical models by mapping the molecular drivers of synaptic damage. Dr. Liebl and his team leveraged their expertise on neuronal signal transmission that occurs across the tripartite synaptic complex, a functional morphological feature involving two neurons, one conducting the signal and the other receiving, and two types of support cells known as glia.

Dr. Liebl’s work established that dysregulation of the molecule D-serine in the synaptic complex contributes to TBI-induced loss of synapses in brain regions distant from the mechanical trauma at the injury site. Specifically, the work of Dr. Liebl and his team established that the substantial synaptic damage in surviving cells after TBI occurs because of a reduction in the normal phasic release of D-serine from the primary neurons, combined with an uncoordinated increase in the production of D-serine from glial support cells.

“Interestingly, D-serine is one of a few D-amino acids with physiological functions in humans, where L-amino acids are the building blocks of our bodies,” Dr. Liebl said. “In a key insight, our team identified that over time, that prolonged
release of D-serine binds to specific receptors on the outskirts of the synapse, activating a process biologically intended to coordinate synaptic pruning in early life but that is improperly turned on by D-serine in TBI.”

Importantly, the team also showed that experimental inhibition of D-serine production or release by glia holds off the synaptic damage and loss that occurs after TBI.

Now that the players and the process have been identified, the team will develop therapeutics to target synaptic loss after neurotrauma. In collaboration with neurosurgeons, they have confirmed that the same molecular machines are involved in humans as in the pre-clinical models.

“Our work will be expanded to confirm calibration of the models and move toward a pharmaceutical agent to target this now well-defined mechanism,” Dr. Liebl said.

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